
Identification of novel long noncoding RNAs underlying vertebrate cardiovascular development.

Journal: Circulation

Publication Year: 2015

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PubMed link: 25739401

Funding Grants: Training in the Biology of Human Embryonic Stem Cells and Emerging Technologies II, Training in the Biology of Human Embryonic Stem Cells and Emerging Technologies, Direct reprogramming towards vascular progenitors for the treatment of ischemia

Public Summary:

BACKGROUND: Long noncoding RNAs (lncRNAs) have emerged as critical epigenetic regulators with important functions in development and disease. Here, we sought to identify and functionally characterize novel lncRNAs critical for vertebrate development. **METHODS AND RESULTS:** By relying on human pluripotent stem cell differentiation models, we investigated lncRNAs differentially regulated at key steps during human cardiovascular development with a special focus on vascular endothelial cells. RNA sequencing led to the generation of large data sets that serve as a gene expression roadmap highlighting gene expression changes during human pluripotent cell differentiation. Stage-specific analyses led to the identification of 3 previously uncharacterized lncRNAs, TERMINATOR, ALIEN, and PUNISHER, specifically expressed in undifferentiated pluripotent stem cells, cardiovascular progenitors, and differentiated endothelial cells, respectively. Functional characterization, including localization studies, dynamic expression analyses, epigenetic modification monitoring, and knockdown experiments in lower vertebrates, as well as murine embryos and human cells, confirmed a critical role for each lncRNA specific for each analyzed developmental stage. **CONCLUSIONS:** We have identified and functionally characterized 3 novel lncRNAs involved in vertebrate and human cardiovascular development, and we provide a comprehensive transcriptomic roadmap that sheds new light on the molecular mechanisms underlying human embryonic development, mesodermal commitment, and cardiovascular specification.

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